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Clinical Use of the Nitrogen Mustards: At the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, N. Y., over 300 patients were treated with nitrogen mustard (methyl-bis compound) between October 1944 and December 1947. The lymphoma-leukemia group contained the largest number of patients, 239. This group included 102 cases of Hodgkin's disease, 66 of lymphosarcoma, and 65 of leukemia. The rest of the series consisted of 48 patients with carcinomas of various kinds, including 33 of the lung, and 16 sarcomas.

There is fairly uniform agreement concerning the value of the methyl-bis and tris nitrogen mustard compounds in relation to the lymphomas and leukemias, and concerning their toxic effects. In the past two years at Memorial Hospital, the Chemotherapy Division of the Sloan-Kettering Institute has been making an intensive study of numerous congeners in the mustard series in an effort to find compounds that would be more effective and less toxic than those now in use. So far none has been shown to be superior to methyl-bis (beta-chlorethyl)amine hydrochloride.

The methyl-bis compound (HN2), packaged in 20 c.c. rubber-stoppered vials, each containing 10 mg. of the substance as a dry powder, is now available to qualified institutional users. Immediately before use, 10 c.c. of sterile physiological saline solution is injected into the vial, and the powder is thus brought into a solution containing 1 mg. of HN2 in each cubic centimeter. The desired dose, which in usual practice has been 0.1 mg. per kg. of the patient's body weight, is then withdrawn into the syringe, and injected intravenously. With careful technic the injection may be made directly from a syringe, or, as preferred by some, the solution may be injected into the rubber tube of an infusion set, through which a small infusion of glucose or saline solution is running rather rapidly. With the syringe technic, it seems advisable to perform the venipuncture with the needle attached to a syringe containing saline solution; then to change to that containing the nitrogen mustard solution; then, after all the nitrogen mustard has been injected, to change back to the syringe containing saline. The two-syringe technic, like the infusion technic, is a precaution for the purpose of minimizing mustard irritation of the vein and overlying subcutaneous tissue.

When the authors began the use of the methyl-bis compound, in October 1944, their first aim was to determine what it could do for patients with advanced cases of Hodgkin's disease that had become refractory to x-ray treatment. Because most of these patients were quite ill, caution was used in the dosage of the drug; in some cases only 0.05 mg. per kilogram of body weight was given, and in others the doses were spaced two or three days apart. The early results in this type of case were rather disappointing. When some of the patients with less advanced cases were treated, however, the results were better.

As experience grew, the side actions to be expected and the doses required to produce therapeutic effects became better known. Whereas, throughout the

country it has been customary to administer 0.1 mg. per kilogram of body weight once a day for four days, the author and associates found that it was desirable in some instances to exceed this amount, using 6 or 7 or sometimes more such single doses. In some few cases the so-called single dose of 0.1 mg. per kilogram was given more than once in 24 hours. The variation of dosage most commonly used in recent months has been the administration of a so-called double dose, that is, 0.2 mg. per kilogram, usually on two successive days, followed in some cases by a similar dose on the third, fourth, or fifth day. This doubling of the dose was based on the observation that it seemed to make the patients no more ill than the single dose, and at the same time had the advantage of shortening the period of hospitalization, cutting in half the number of possible systemic reactions in any given case, and decreasing the number of venipunctures and hence the risk of chemical phlebitis or an accidental perivenous inflammatory reaction.

Dosage is guided largely by the total white cell count. In cases of Hodgkin's disease or lymphosarcoma, for example, if the white count is normal or elevated, and other circumstances are favorable, it is felt usually that it is safe to give 3 double doses, a total of 0.6 mg. per kilogram of body weight, and that a considerable leukopenia should be expected to follow within from a few days to a week as a measure of adequate dosage.

In some cases a full course of treatment may be repeated in a month or two. In other cases because of a continuing low white cell count, another full course cannot be used, and in such instances only one dose of 0.2 mg. per kilogram or two or three doses of 0.1 mg. per kilogram may be decided upon as the maximum safe amount.

Both Jacobson and Wintrobe have reported on maintenance therapy in certain cases, consisting of the administration of a total of from 0.2 to 0.3 mg. per kilogram in divided doses every few weeks. At Memorial Hospital this plan has not been tested extensively. In general, signs and symptoms of beginning relapse have been awaited before the patient has been subjected to another course of the drug.

Toxic effects are both local and general, the latter being chiefly gastrointestinal and hematologic. Some of the congeners of HN2 have produced cerebral toxic effects, but these are practically never seen with therapeutic doses of HN2. Great care must be taken to avoid introduction of even the slightest amount of nitrogen mustard into the tissue outside the vein, because it will cause pain, and produce an area of swelling, redness, and induration that will continue to be painful and last for from weeks to months and may even slough. Even with careful technic the vein may become thrombosed. The tris-compound will often cause marked thrombosis. These thromboses are annoying but so far have not given rise to perceptible embolic phenomena. All venipunctures, for whatever purpose, in a patient who may need to be treated by nitrogen

mustard should be done with a view toward saving the patency of the veins, for in some patients the readily available sites for venipuncture have been used up.

The gastro-intestinal toxic effects are mainly nausea and vomiting. Nausea is felt by most patients in from one to several hours following the injection, and about half the patients will retch and vomit. These symptoms may last for several hours, but in nearly all cases the patient is ready to accept another injection by the next day. In a series of daily injections it has been noted that the reaction is most severe following the first injection. In some patients there has been little or apparently no gastro-intestinal disturbance. Diarrhea is uncommon. Pyridoxine hydrochloride injected intravenously (or preferably intramuscularly in order to save the veins) in from 10 to 30 minutes following the nitrogen mustard seems to allay the gastric symptoms in some patients. The two drugs are not given simultaneously nor is pyridoxine administered first, because it has been listed by Gilman as one of the substances with which nitrogen mustard reacts. Since the reaction of nitrogen mustard with cells is believed to take place within 5 minutes, a delay of from 10 to 30 minutes before giving pyridoxine should be ample to prevent it from competing with the tissues. Vomiting may naturally be hazardous in a patient with a marked hemorrhagic diathesis. In a young man who had an aggressive lymphosarcoma, a diffuse purpura of the whole head and neck developed as a result of straining during vomiting after an injection of nitrogen mustard. One patient with acute leukemia died, apparently of intracranial hemorrhage, after vomiting following an initial injection of the drug. Patients who vomit repeatedly for from 4 to 7 days may require electrolyte and fluid replacement. One striking sequel to a course of nitrogen mustard, particularly in patients who are benefited by a rapid drop of fever and relief from toxic symptoms, is the appearance of an enormous appetite and rapid increase in weight.

Toxic effects on the hematopoietic system are unavoidable with therapeutically effective doses of nitrogen mustard. The white cell count often shows a fall even before completion of the course of injections. In general, a lymphopenia is followed rapidly by a granulocytopenia, so that within a week or so the total white count may be down to 1,000 cells per cubic millimeter or less. Usually, when the white cells reach so low a level, penicillin is given parenterally, supposedly as a prophylactic against infection. It seems to be the general experience that very few agranulocytotic lesions develop in patients with these extremely low white cell counts. In from 2 to 4 weeks the white count usually shows fair return towards normal, although in some of the more seriously ill patients, with Hodgkin's disease or lymphosarcoma, there has been a prolonged leukopenic effect. In these seriously ill patients particularly, the marrow may appear to be severely depressed by a second course of nitrogen mustard, and a prolonged leukopenia may ensue.

The platelets at times seem at first to be somewhat increased in number, but usually they drop below normal levels. The count is often well below

50,000, without much, and in some cases without any, evidence of bleeding tendency; on the other hand, sometimes purpuric spots may be seen with a platelet level well above 50,000. A drop in red cell and hemoglobin values may occur rapidly in patients having a severe toxic reaction to nitrogen mustard, but, in probably the majority of cases, it may be questionable whether the anemia is not rather an expression of the state of the patient's disease prior to nitrogen mustard therapy, plus the effects of loss of nutrition. An increase of reticulocytes in two or three weeks following the series of injections of nitrogen mustard may herald an improvement in the red cell count.

After over three years of intensive daily experience with nitrogen mustard, and with its use in the treatment of over 300 patients, some fairly definite opinions have been formed.

Hodgkin's Disease. One hundred and two patients with Hodgkin's disease have been treated. The author now regards nitrogen mustard as an indispensable adjunct for the palliative treatment of this disease, but by no means believes that it replaces x-ray therapy. Two groups of patients are still best treated by x-rays without nitrogen mustard; they are (1) those with the disease confined to one group of nodes, in whom early aggressive irradiation should offer a hope for either cure or very long control (and in some of whom perhaps radical surgery should be employed); and (2) those showing beginning spread, but in whom the disease is still relatively regional and without marked constitutional symptoms. In this latter group, x-ray treatment will usually give better results if it is well designed, precisely administered, and adequate in dosage. It is in a third group, in which actual generalization has occurred and constitutional symptoms (fever, night sweats, and itching) have appeared, that nitrogen mustard will find its best use. Even in these cases there is usually a place for x-ray therapy, either in conjunction with the course of nitrogen mustard, or as interim treatment of bulky residual nodal masses or bone lesions. Some of these patients with generalized spread will do so well following a course of nitrogen mustard but at the same time have such low white cell counts as a result of its use that x-ray treatment is deferred.

The beneficial effects of nitrogen mustard in Hodgkin's disease are a rapid drop in fever, a relief of toxic symptoms, and a varying shrinkage of granulomatous masses and infiltrates. If the spleen is enlarged, it may shrink measurably. Infiltrations in the lung may nearly disappear. In one patient with paraplegia and partial paralysis of the upper extremities, the decrease of neurological signs was as rapid as could be expected with the best results of x-ray therapy over the spinal cord. In some cases pain associated with bone involvement has diminished or disappeared, but healing of osseous lesions, such as may follow local x-ray therapy, has not been obtained with nitrogen mustard. Nor has the itching of Hodgkin's disease been relieved as well as would be hoped. The duration of remissions produced by the author's usual method of giving nitrogen mustard in a concentrated course and then awaiting signs of relapse has all too often been disappointingly short. This leads to the thought that further trial of maintenance therapy by judiciously spaced small doses should be undertaken. Despite

its shortcomings, nitrogen mustard has been a valuable aid in the palliation of generalized Hodgkin's disease.

Because nitrogen mustard has such a marked effect on generalized Hodgkin's disease, why not employ it in the earlier cases in conjunction with roentgen therapy, in the hope of obtaining superior results? The practical objection at present to this plan is that the entire patient is poisoned for the sake of an effect on a local process, which it is known will almost always respond better to local irradiation, and in most cases the leukopenia resulting from the nitrogen mustard would probably contraindicate the delivery of an adequate dose of roentgen rays. Perhaps it might be worth while to give a small dose of nitrogen mustard, say 0.1 or 0.2 mg. per kilogram of body weight, to some patients in the early or intermediate stages of Hodgkin's disease a month or two after they have been treated adequately by local irradiation.

Lymphosarcoma. Lymphosarcoma, for which 66 patients have been treated, may respond to nitrogen mustard injections with rapid though usually incomplete remissions, and in the more aggressive forms of the disease a rapid relapse is the rule, and continued growth of tumor may be seen despite dangerously large doses. Occasionally the use of nitrogen mustard may be a life-saving procedure when other measures seem contraindicated. An example of this concerned an elderly woman with lymphosarcoma, which, growing diffusely in the side of the neck, was fixed to the larynx and trachea, and extended throughout the region of the thyroid gland and down through the upper thoracic aperture. She was orthopneic and had marked stridorous respirations. The surgeon believed tracheostomy would be useless, because he would have to cut through about an inch of tumor tissue overlying the trachea and it was evident that there would continue to be obstruction well below the level of the operation. It was thought that roentgen therapy would be useless and probably dangerous because a large dose, to get a quick effect, would probably cause complete obstruction of the airway, and fractionated doses would be so slowly acting that death would occur before the obstruction could be relieved. As for nitrogen mustard, it was feared that the patient, who was struggling for every breath, would be in a great danger of aspirating vomitus and being asphyxiated. It was decided, however, that this risk seemed less than that of either tracheostomy or irradiation. The effect of one injection of 0.2 mg. per kilogram seemed little short of miraculous, for the next morning the patient was evidently out of immediate danger. Further injections of nitrogen mustard were given, and then local roentgen treatment to the neck during the next ten days, with the result that the tumor completely disappeared for several weeks, and the patient's life was temporarily spared.

In some of the less acute or agressive lymphosarcomas and in some lympholeukosarcomas, large doses have produced remissions of from a few months to a year or more.

If, as Gilman states, the action of this drug is similar to that of irradiation, the result of its use for follicular lymphoma should be a prompt and long lasting remission. The somewhat mediocre results in a few cases which on biopsy of a peripheral node have been called follicular lymphoma are to be explained on the same basis as the not infrequent failure to produce complete and durable remissions in some such cases by means of roentgen therapy, namely, that biopsy of a peripheral node revealing follicular lymphoma may sometimes be misleading, in that much of the disease (in other areas) has progressed to reticulum-cell sarcoma.

Leukemia. Sixty-five patients with leukemia have been treated: 17 with acute leukemia, 1 with monocytic leukemia, 17 with chronic lymphatic leukemia, and 30 with chronic myeloid leukemia. Nitrogen mustard can lower the white cell count and in some cases will reduce the size of the spleen or lymph nodes strikingly, so that the result at first seems about like that produced by roentgen treatment. In general, the remissions in chronic leukemia are of short duration - a month or so - and usually the differential count is not much altered. In the typical case of chronic myeloid leukemia with the characteristically large spleen, it would seem that, as a rule, a longer remission and one accompanied by greater reduction in the splenomegaly can be produced, initially at least, by x-ray treatment of the spleen. Not often does one see rapid gains in the red cell count and hemoglobin following nitrogen mustard therapy of chronic myeloid leukemia to the degree that these gains are seen following an initial course of x-ray therapy.

In the acute leukemias no great beneficial effect can be reported. Symptomatic and objective relief may be seen but are of very brief duration, and blast forms persist in the blood.

Carcinoma of the Lung. Thirty-three patients with bronchial carcinoma have been treated. The first two such patients showed a dramatic response. The first patient treated had an oat-cell carcinoma, obviously unsuitable for either surgery or irradiation, and was placed on the critical list immediately upon admission because he was evidently doomed to die within two or three weeks, judging by the rapid course and extent of the disease and the symptoms. Never before in all the author's experience with such a cancer of the lung in this stage had he witnessed a reversal of the expected rapid downhill course. Relief of symptoms took place within a few days. Shortly afterward a similar patient was treated, with a similar result. The effect was by no means curative. In fact, it was difficult to see a great deal of improvement on the x-ray films, except for resorption of pleural exudate in the first case. Subsequently, in other cases of such lung cancer with enlarged supraclavicular nodes due to metastatic cancer, and in which the disease had not reached the terminal phase, prompt relief of signs and symptoms of mediastinal block and decrease in size of the involved nodes were observed. Usually, these partial remissions have not lasted more than a few weeks unless million-volt roentgen therapy to the intrathoracic part of the tumor and 250-kv. therapy to the metastatic tumor

in the neck nodes have been given following the nitrogen mustard. When that is done, the remission, though still only partial, may be of somewhat longer duration. Nevertheless, as a means of palliation in cancers of the lung showing marked anaplasia, a course of HN2, followed by roentgen therapy, has seemed well worth while. In the more routine types of bronchogenic cancer, it is difficult to say that it has produced any better results than roentgen therapy alone.

Other Types of Cancer. About 15 other carcinomas of various kinds and 16 miscellaneous sarcomas have been treated. From slight to moderate palliation has been observed in some cases.

A limited experience with mycosis fungoides (4 cases) suggests that patients with the chronic type without bulky tumors of the skin may do fairly well, but that in the advanced or aggressive cases, although striking and rapid partial remissions may occur, they will probably be followed by rapid relapses, even in the face of dangerously large toxic doses. Only two patients with polycythemia vera have been treated in this series. They seem to have responded very favorably.

Summary of Results. To sum up the observed results in over 300 patients treated at Memorial Hospital by nitrogen mustard, the following statements may be made:

1. None of the nitrogen mustards so far used has given any indication of ability to cure any of the types of cancer treated.

2. Palliative results of nitrogen mustard therapy have nevertheless been so marked in certain types of cancer as to make the author and associates consider this new therapeutic agent indispensable. These types are: (a) generalized Hodgkin's disease with marked constitutional symptoms; (b) advanced lymphosarcoma in which some part of the disease is immediately threatening to life and in which the lesion causing the immediate danger is not amenable to surgery or irradiation; (c) the anaplastic carcinomas of the lung.

3. In early and intermediate stages of Hodgkin's disease, in most cases of lymphosarcoma, and in most cases of chronic leukemia, it seems doubtful that nitrogen mustard offers any advantage in general over other methods of treatment, particularly over roentgen rays, or in fact whether, in general, it is as good an all-around agent as roentgen rays.

4. Since only a few of the hundreds of possible nitrogen mustard compounds have been tried extensively enough clinically, it may be that other compounds will be found that will be at the same time less toxic and more effective in a broader range of cancers. (Radiol., April '48 - L. F. Craver)

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Atypical Adynamic Ileus Apparently Caused by Nutritional (Thiamine Chloride) Deficiency: During the past 5 years, the author has observed 4 instances of severe abdominal distention, in which the clinical history, physical findings, and response to therapy strongly suggested that the adynamic ileus was caused by serious nutritional deficiency. Review of 2 additional cases with similar clinical courses, which had not been satisfactorily explained at the time of previous observation indicated that they belonged in the same group. These six cases may represent a distinct clinical entity of special interest to surgeons, since in them the abdominal distention is so pronounced that acute intestinal obstruction is suspected.

In the first case in which the condition was recognized as resulting from vitamin deficiency, the patient had a sore mouth which directed attention to this possibility, and specific questions brought to light a history of chronic alcoholism. In this instance, a preoperative diagnosis of "annular carcinoma of the sigmoid" had been made on the basis of obstructive symptoms and the roentgenographic findings, but no such lesion was found at operation. However, the abdominal distention increased after operation and was not brought under control until vitamin therapy was instituted. The second patient, also an alcoholic, was subjected to celiotomy for "acute appendicitis," but at operation there was so much intestinal distention that the appendix was not readily accessible and was not removed. When uncontrollable distention continued after operation, the experience in the first case was recalled, and vitamin therapy was instituted, with equally striking results.

Both patients in the two earlier unexplained cases that were later reviewed were alcoholics. In one, celiotomy had been performed because of a mistaken diagnosis of acute appendicitis, but no pathologic evidence had been found in the appendix to account for the symptoms. Adynamic ileus had progressed after operation, with severe alcoholic delirium, to a fatal outcome. In the other, severe distention had developed after an inguinal herniorrhaphy, but had disappeared without the administration of thiamine chloride.

The two additional patients observed were not alcoholics, but had been on greatly restricted diets - in one instance for biliary disease, and in the other for weight reduction. In these cases, no operation was performed, because nutritional deficiency was recognized as the cause of the distention, and the response to the administration of thiamine chloride and vitamin B complex was striking and complete.

One of the six case histories included in the original article follows:

Case 6. A man, aged 53, consulted his physician for an annual health examination. He had complained of no illness, but was overweight. After a complete examination, including an electrocardiogram and roentgenologic study of the gastro-intestinal tract and gall bladder, and a sigmoidoscopic examination, all of which yielded normal findings, his physician recommended a restricted diet for several weeks, but was not satisfied with the rate of weight loss and so restricted his diet to the following: breakfast - 1 slice of toast, organge or grapefruit, black coffee; luncheon - meat, fresh fruit; dinner - meat, vegetables (which included only lettuce, spinach, carrots, and peas), and canned fruit.

On this diet he lost approximately 20 pounds in 2 months. During this period, he tired easily and felt exhausted most of the time. He felt that he was not so keen mentally, was irritable, and suffered from pains in the calves of the legs. His abdomen became bloated and distended and bowel evacuations occurred two or three times a day, but these did not relieve the distention. Finally, the distention increased enormously and respiration was embarrassed; at this point the patient became alarmed and consulted the author. Except for the tremendous abdominal distention, physical examination revealed nothing abnormal. Although the patient complained of considerable distress, there was no belching, passing of flatus or actual pain. Because a health examination, including a complete gastro-intestinal and gall-bladder roentgenologic study and a sigmoidoscopic examination had recently been made, it was concluded that this patient was suffering from an acute adynamic ileus on a nutritional basis (thiamine deficiency). Thiamine chloride, 100 milligrams, was administered intravenously, and repeated in 4 hours; this regimen produced complete relief in 12 hours. The injections were continued daily for several days, and the nervous symptoms, leg pains and irritability disappeared completely. Bowel evacuations decreased to one a day. The patient received dietary instruction and therapeutic doses of vitamin B complex orally. His general health has remained excellent, with no recurrence of gastro-intestinal symptoms. The patient says that he feels much more alert and has never been more fit in his life.

Despite the enormous number of clinical and experimental studies on nutritional deficiencies that have been reported during the last few decades and the increasing preciseness of knowledge concerning them, it would appear that numerous clinical problems associated with these disorders remain to be elucidated. So far as could be ascertained by a search of the Quarterly Cumulative Index Medicus for the past several years, the exact clinical syndrome here described has not been previously reported, even though the recognition of digestive symptoms as a phase of vitamin B deficiency has been well established clinically and roentgenologically. In previous reports, however, there has been no emphasis on the fact that severe and uncontrollable abdominal distention, which might lead to erroneous surgical diagnoses and needless operations, may be the result of vitamin B deficiency.

The roentgenologic studies made by Golden have stimulated interest in the relationship of vitamin deficiency to intestinal motility and the so-called "deficiency pattern" of the small intestine is a fairly well defined radiologic entity. However, as Golden has emphasized, the roentgenologic findings are not constant and appear to vary with the severity and duration of the nutritional disorder. In earlier, less advanced stages, the barium passes rapidly through the jejunum, reaching the lower part of the small intestine in 15 minutes and entering the cecum in less than half an hour; the lumen is reduced to one half or even one fourth its normal width. In more advanced stages, movement of barium through the intestine is slow, and the lumen may vary from normal to more than twice normal width. Dilated loops are characteristically seen in well advanced stages, which are usually designated clinically as nontropical sprue. There is abnormal segmentation owing to areas of spasm of variable length, sometimes completely expelling the opaque material from the contracted area, giving the impression of a discrete mass. A scattering effect may be caused by small irregular masses of barium left behind as the main mass of barium passes along. In more advanced stages, gas and fluid levels on plain abdominal roentgenograms may suggest the possibility of ileus. The most marked and persistent changes are localized in the middle third of the small bowel.

Experimentally, it has been demonstrated that cholinergic nerves liberate not only acetylcholine but also thiamine, when stimulated, and that thiamine increases the effect of acetylcholine on the intestine and circulatory apparatus of the cat. Chemically, acetylcholine and thiamine chloride are closely related compounds, and hence may function synergistically. It seems probable that these facts furnish clues concerning the mechanism of production of adynamic ileus in the presence of thiamine deficiency, and concerning the striking therapeutic response to administration of thiamine chloride parenterally.

In the cases in this series, the characteristic pathologic changes encountered were edema and thickening of the intestinal walls, with engorgement of the blood vessels. In fatal cases of deficiency disease, in which roentgenologic changes have previously been demonstrated in the intestine, atrophy of the tunica muscularis and mucosa, edema, round cell infiltration and fibrosis of the submucosa, and ulceration have been described.

The type of pathologic changes in the intestine, and the variety of gastrointestinal symptoms that have been described in deficiency states, suggest that a nutritional disturbance should be suspected in any case in which the digestive symptoms, clinical and radiologic findings seem atypical or anomalous. In this way the cause of certain obscure gastro-intestinal conditions might be elucidated. It may even be justifiable to raise the question of whether nutritional deficiency may play a role in the causation of at least some cases of so-called nonspecific regional enteritis, especially in view of Owen's recent pathologic study, which showed neuromuscular hyperplasia as a characteristic feature of this condition, not previously reported by others.

The experience with these cases suggests that nutritional deficiency should be suspected, and a therapeutic trial of vitamins made, in cases of abdominal distention in which the evidence does not justify a positive diagnosis of mechanical obstruction of the intestines. In 4 of the author's 6 cases, the distention was not controlled by mechanical decompression or administration of prostigmine, but responded dramatically to the administration of thiamine chloride and vitamine B complex. This experience suggests also that thiamine chloride should be administered at the time of operation to prevent postoperative distention, especially in patients whose nutritional status is at all questionable or in whom there is any suspicion of liver damage. It is now the author's routine practice to administer parenterally vitamin B complex with high thiamine content to all surgical patients the day before operation, and daily for 3 days after operation. Since this has been done, postoperative distention has been almost entirely eliminated. (Surg., Gynec. and Obst., May '48 - D. J. Leithauser)

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Sudden and Unexpected Natural Death: This is the second in a series of papers on sudden and unexpected natural death, verified at necropsy, in 2,030 consecutive cases in the Office of the Chief Medical Examiner, New York City, for the Borough of Manhattan.

Death was sudden because it took place usually within 24 hours after the onset of symptoms, and unexpected in that the victims were apparently healthy at the time of death. The designation "natural death" indicates that death resulted exclusively from disease unassociated with external violence or poisoning. The 2,030 cases were observed during the period from 1 January 1937 to 30 June 1943.

The material was gathered from a community the population of which is made up of all races and includes relatively many adults. The Census Bureau records a total population, in 1940 in Manhattan, of almost 1,900,000, of which 51 percent were women; the same sex distribution holds true for the 1,580,000 white persons. Among the 298,000 Negroes, women totaled over 55 percent, but for the other races, largely Asiatic, there were but 2,186 (15.6 percent) women compared with 11,748 men. The preponderance of adults in the population is striking; slightly more than three fourths of all persons on Manhattan Island were over 21 years of age. When it is recalled that at any given time New York City normally has about 500,000 visitors, most of whom are adults, and that the majority of them spend their time in Manhattan, the reservoir from which material for this study was collected is overwhelmingly composed of mature individuals. Also, during the working day, many adults from the other four boroughs of the city and from suburban communities add to the fixed population of Manhattan.

Diseases of the heart and aorta were first among the causes of death (45 percent), and were succeeded, in order, by diseases of the respiratory tract (23 percent), nervous system (18 percent), digestive organs (6.2 percent), urinary tract (almost 2 percent), and genital apparatus (1.3 percent). A miscellaneous group accounted for 4.4 percent of the deaths.

The role of coronary arteriosclerosis in this series is best illustrated and emphasized by the fact that in almost one third (30.4 percent) of the 2,030 cases, death was caused by that disease. There is much misunderstanding of the symptomatology and manner of death, in relation to the fatal lesions in this disease, which has been responsible for medicolegal confusion. Responsibility for the misunderstanding may be attributed in part to the lack of appropriate data from medicolegal authorities; a share in the culpability belongs to those clinicians who attempt to evaluate coronary artery disease, in which there have been no premortem symptoms, on the basis of experience with the more common examples encountered in office and hospital practice. Pathologists are not without blame, for, like clinicians, they also have too readily analyzed their material with criteria gained from autopsies of patients dying after days or weeks in the hospital. It cannot be overemphasized that the problems confronting the medical examiner in sudden and unexpected natural death, of whatever cause, require standards of evaluation with which the clinician and hospital pathologist are not entirely familiar.

It should be pointed out that the finding of a severe grade of sclerosis of the coronary arteries does not, per se, mean that such disease is the cause of death.

Death should not be attributed to diseases of the coronary arteries without a complete study of the circumstances and a full autopsy, including examination of the brain, and, when necessary, chemical examination of organs. In the absence of significant changes in organs other than the heart, with chemical findings unrelated to the death, and with a review of the manner of death (not always available), death may be ascribed to coronary artery disease when such disease is present and in adequate degree. Mistaken diagnoses will result from failure to observe all these criteria.

In addition to the present study, the only report available on coronary artery disease as a cause of sudden and unexpected death in a comparable large urban civilian population is that of Hallermann, whose monograph appeared in 1939. During a five-year-period (from 1931 to 1935) at the Berlin Institute for Legal and Social Medicine, there were 6,481 necropsies in the noncriminal category.

Coronary artery disease as a cause of sudden death is almost exclusively a malady of white men; only 6 percent (36 cases) of the subjects were women and these were only of the white race. A single Asiatic and 23 Negroes (3.7 percent) were found among the male subjects, thus making the white male contribution to coronary artery sclerosis slightly more than 90 percent. There is a striking disparity between the 3.7 percent of male Negro cases and the 14.5 percent representing the proportion of the male population which they formed. The discrepancy remains great even if all of the visitors to Manhattan are considered as white, and as men, thus reducing the Negro male population to 9.4 percent. Lest it be thought that there is a relative immunity of Negroes to sudden and unexpected death from cardiac disease, it may be pointed out that, of the 46 cases of death attributed to obstruction of the coronary ostia in syphilitic aortitis, 18 (39 percent), or two and one half times the expected percentage, were Negroes. Syphilitic aortitis, however, does not come within the scope of this paper.

Of the 617 instances of coronary artery sclerosis, in almost three fourths (73.3 percent) no associated fresh thrombosis of the vessels could be grossly demonstrated. This approximates the 95.3 and 80.2 percent for two periods mentioned in Hallermann's Berlin study. In most cases, atheromatosis with or without calcification had produced significant diminution of luminal caliber, so that, physiologically as well as anatomically, the effect was not different from that of old thrombosis. Functionally a narrowed sclerotic vessel, even without complete occlusion of the passage, may be inadequate in furnishing a satisfactory blood supply to the myocardium. From the statistical viewpoint, therefore, sudden, unexpected natural death from coronary artery disease is best recorded simply as "coronary artery sclerosis."

Hearts showing nonthrombotic coronary artery sclerosis were free of fibrosis of the myocardium in 45 percent and were associated with fibrosis in only

50 percent; infarction occurred in only 5 percent. The Berlin statistics differ sharply from these values, since nonthrombotic sclerosis was associated with myocardial fibrosis in over 80 percent of the cases, a difference in part attributable to the personal interpretation of the prosector concerning what constitutes "fibrosis."

Slightly more than one fourth of the instances of coronary artery sclerosis were complicated by fresh thrombosis. In 75 percent (in the Berlin series, 60 percent) of the cases of thrombosis infarction of the myocardium was shown both with and without antecedent fibrosis in almost equal proportions.

In an attempt to obtain further clarification, more detailed information was obtained from the protocols of the cases studied during 1938 and 1939. Every profession and trade was represented, with the more humble callings expectedly predominating. In almost one half of the cases (47 percent) death took place in the street, or while at work, or in a public place; in an equally large proportion, the scene was the home or a hotel room. In the home, the bed (17 percent) was as often the place of death as all other parts of the house combined (kitchen, bathroom, and so forth, 17 percent). Those who died in hotels were generally found dead in bed, although not always following a night of rest and relaxation.

How much time elapses between onset of symptoms and death? Because a little more than one third of these persons were found dead in bed, the time element is unknown in that large portion. Of the remaining slightly less than two thirds, in which the period is known, almost 80 percent died virtually instantly. Of the remainder, more lived beyond an hour than died in less than that time.

What relationship, if any, has the drinking of alcoholic liquors in the precipitation of death in coronary artery disease? In slightly less than 75 percent of the autopsies, during the years under closer examination (1938 and 1939), alcohol determinations were done on liver or brain, chiefly the latter; four fifths of these gave negative results. Of the remainder, 35 percent gave results of 1 plus or a trace. It seems evident, then, that acute alcoholism plays no obvious role in the promotion of death in this disease. (Am. Heart J., April '48 - S. M. Rabson and M. Helpern)

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The Electrocardiogram of Man in Semistarvation and Subsequent Rehabilitation: Previous studies by the authors revealed that profound changes in the heart occur in normal persons when they are semistarved and subsequently when they are rehabilitated. This study concerns an analysis of the electrocardiographic findings associated with the observed heart changes. The results confirm the general observations of decreased QRS and T-wave amplitude in electrocardiograms of persons in famine areas; however, the latter have only the character of occasional observations in patients, but in this study quantitative relationships were obtained under controlled conditions.

In 32 normal subjects, electrocardiograms were taken at regular intervals during a control period of three months, during a semistarvation period of 6 months in which a 24-percent weight loss was produced, and during a controlled rehabilitation period of 12 weeks. In 20 subjects, electrocardiograms were taken also after 32 weeks of rehabilitation; the last 20 weeks they were on a freely chosen diet. For estimation of the over-all magnitude of the QRS complex and the T-wave, the sum of the amplitudes in Leads I, II, and III were calculated. The symbols Σ_{QRS} and Σ_T are used to express these values.

During semistarvation, statistically highly significant changes occurred in most phases of the electrocardiogram, and for the majority of subjects the electrocardiograms became clinically abnormal.

There was pronounced slowing of the heart rate, and its variability range decreased both relatively and absolutely so that the heart rate was more regular in semistarved subjects. These changes reached their maximum at their twelfth week of semistarvation, and recovered slowly during their rehabilitation.

Q T interval and mechanical systole duration increased during semistarvation of the subjects and shortened again during their rehabilitation, but these changes lagged behind the simultaneous changes of the cycle length in both directions, so that K_{Q-T} and K_{SYST} changed accordingly.

The amplitudes of all deflections (P wave, QRS complex, and T wave) decreased continuously and very considerably during semistarvation of the subjects and recovered slowly during their rehabilitation.

During semistarvation of the subjects there was a marked right axis shift of the QRS axis and even more so of the T axis, so that the angle between both axes was diminished. During their rehabilitation, both QRS axis and T axis moved to the left, overshooting the original prestarvation position at the thirty-second week of semistarvation.

Most phases of the electrocardiogram showed only partial recovery during 12 weeks of rehabilitation in the subjects, but were back to the control values within 32 weeks, several functions (heart rate, R_1, Σ_T, QRS axis, T axis) overshooting the control values subsequently.

There was a discrepancy in the time course of changes between interval and amplitude changes, and between QRS complex and T-wave changes.

There was no correlation between QRS axis changes and anatomic axis changes, or between QRS axis and T axis, although all changed in the same direction.

A statistically significant differentiation of the groups of subjects receiving different caloric levels during rehabilitation was obtained in the following items: systole duration, K_{QT}, R_1, R_2, Σ_{QRS}, T_1, T_2, Σ_T, and T axis.

Before their semistarvation, voluntary maximal inspiration produced an initial acceleration of the heart rate in all subjects, which was followed by a late retardation in 18 subjects. During their semistarvation, the effect of maximal inspiration was diminished in respect to both initial acceleration and late retardation. During their 12 weeks of rehabilitation, only the late retardation was restored. The decrease of KQT and KSYST in the late phase of maximal inspiration was significantly less pronounced at the end of their semistarvation, and this effect was, to a certain degree, independent of the changes in the heart rate.

Although the slow heart rate in semistarved persons, as a rule, was due to sinus bradycardia, in two subjects nodal rhythm was observed; this was temporarily restored to sinus rhythm during maximum voluntary inspiration.

Amplitude Changes. The decrease of the QRS and T-wave amplitudes is probably the most significant change in the electrocardiogram of starving persons. It may be due to the following causes:

1. Decrease of Heart Size. The decrease of the amplitudes occurred simultaneously with a very marked decrease of the heart size as determined by teleroentgenograms and roentgenkymograms. Evidence from autopsy material indicates that the heart weight decreases in semistarvation much in proportion to the loss of body weight. Since in the hypertrophic heart the QRS amplitude is, as a rule, increased, it might seem logical to assume that a decrease in an atrophic heart would be explained on this basis alone. However, this assumption should not be made without reservations, since secondary changes in the hypertrophic heart, which are absent in the atrophic heart, might be contributory.

2. Myocardial Degeneration. There is evidence of widespread degenerative histologic changes in the hearts of starved animals which has been confirmed recently by Pollack in human autopsy material.

3. Decreased Metabolic Rate. Although there is no outright correlation between QRS amplitude and the basal metabolic rate, both QRS and T amplitudes are usually decreased in the electrocardiograms of persons with hypothyroidism and have a tendency to be increased in persons with hyperthyroidism. The average basal metabolic rate of the subjects in this study decreased 37 percent during semistarvation, and at R12 was still only 82 percent of the prestarvation control.

4. Fluid Accumulation in Chest or Pericardium. Although 28 out of 32 of these subjects showed clinical edema during semistarvation there was no evidence to indicate an accumulation of fluid in the chest or pericardium.

Axis Changes. The right axis shift of the QRS complex was probably due to positional changes; a smaller heart tends to assume a more vertical position.

A right axis shift of the anatomic axis was obvious in the roentgenographic studies. However, there was no exact correlation between the right axis shift of the anatomic axis and the QRS axis; this discrepancy might be due to the fact that the roentgenographic studies were made with the subjects in the standing position, although the electrocardiograms were taken with the subjects in the supine position.

It is also possible that the right axis shift of the QRS axis is due to a relative right ventricular preponderance or to a change in the pathway of excitation. A relative right ventricular preponderance could be produced by a greater degree of atrophy in the left ventricle; there are no data available to support or to contradict such assumption. In this connection, it is interesting that in Tur's material right axis shift was more common in the advanced cases than it was in the milder cases. The main reason for the overshooting of the left axis shift during rehabilitation is probably mechanical for (1) all men were fatter, particularly in the abdominal region, at R32 than they were at C, and (2) the increased volume of the abdominal organs would explain a position of the axis farther to the left.

Heart Rate. The slow heart rate in semistarved persons is referable to a sinus bradycardia in most cases, but this study shows that in exceptional cases nodal rhythm occurs. The occurrence of nodal rhythm would be compatible with the assumption that the slow heart rate in semistarved persons is due to increased vagus tone. Schiff reported that atropine (from 0.5 to 0.75 mg.) promptly abolished starvation bradycardia for a transitory period, but Schittenhelm and Schlecht found no effect whatever with 1.0 mg. of atropine. The authors found not only the late vagus effect, but also the early sympathetic acceleration of the heart rate to be decreased in maximum inspiration. Since both vagus and sympathetic response are diminished, the slow heart rate may be due to both increased vagus tone and loss of sympathetic tone. This would agree with Hoesslin's observations of the absence of emotional pulse rate changes in semistarvation in man and with the authors' findings of the decreased range of variability.

Jordan's observation that the initial digitalis retardation of the heart rate fails to appear in starving dogs is an interesting corroboration of these results. Statkewitsch's findings of extensive pathologic changes in the cardiac ganglia of rabbits in advanced inanition might be regarded as histologic evidence for the loss of vegetative regulation which would only be very slowly reversed in rehabilitation.

Except for the beriberi heart, the condition of the heart in states of malnutrition has found little attention in clinical medicine. In several recent textbooks of cardiology, no mention is made of the importance of the nutritional state for cardiac pathology. Vaquez recognized the theoretical importance of nutritional effects on the condition of the myocardium, but he was inclined to believe that the effect is insignificant. Although in general there is little correlation between electrocardiographic findings and the functional state of the heart, the

occurrence of significant changes in most phases of the electrocardiogram during semistarvation in man cannot be ignored. It seems safe to conclude that they indicate myocardial changes. The implications of the present results would be that prolonged semistarvation produces a deterioration of the state of the myocardium, which might be compensated for functionally for a time. However, the compensation might break down under conditions of additional stress. In the present study such stress conditions were excluded, but they might well arise under less well-protected conditions. In connection with this, it is interesting to note that one of the subjects in this series suddenly became decompensated in the early rehabilitation period; the heart became enlarged and the venous pressure rose abruptly. Treatment with bed rest, reduced food intake, and diuretics restored the patient within one week. The reason the decompensation appeared in the rehabilitation period might be the increased circulatory load due to sharply increased food ingestion and greater activity. (Am. Heart J., April '48 - E. Simonson et al.)

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Cerebral Complications in Pertussis: Pertussis is still a challenge to the medical profession, especially when it occurs in infants under one year of age. The disease is most serious when complicated by pulmonary or cerebral manifestations.

Over 200,000 cases of whooping cough are reported annually in the United States, with from 5,000 to 7,000 deaths. The high incidence among infants under one year, and the high mortality rate in this group are especially striking. The late sequelae in this disease have been infrequently described in the literature, although they occur in a large number of the patients.

A great variety of cerebral complications in pertussis have been described. Clinical findings have included convulsions, monoplegia, hemiplegia, diplegia, paraplegia, deafness, blindness, aphasia and idiocy. Pathologically, meningeal and cerebral hemorrhages, meningitis, encephalitis, and thrombosis of cerebral veins and cerebral sinuses have been observed.

The purpose of this paper is to present an analysis of 47 cases of clinical cerebral complications which occurred in 6,002 patients with pertussis admitted from 1932 to 1946 inclusive to the Kingston Avenue Hospital for Communicable Diseases, Brooklyn, N. Y. (The incidence of cerebral complications in pertussis cannot be definitely established because not all patients with pertussis in a community are hospitalized.)

During the years from 1932 to 1938 inclusive, 2,758 patients were admitted and 261 died, making a general mortality rate of 9.4 percent. In 24 cases there were cerebral complications. Six patients died, making a mortality rate among these of 25 percent.

From 1939 to 1946 inclusive, 3,244 patients were admitted and 109 died, making a general mortality rate of 3.3 percent. Twenty-three cases were complicated by cerebral manifestations and 13 patients died, making a mortality rate among these of 56.5 percent.

Of the 47 patients with cerebral complications during the whole period from 1932 to 1946 inclusive, 28 survived and 19 died, making an average mortality rate of 40.4 percent. The onset of cerebral complications was almost always accompanied by convulsions and a sudden rise in temperature. Fifty percent of the patients who developed cerebral complications were under one year of age, and 60 percent were under 2 years of age. In 72.5 percent of the patients, the onset of the cerebral complications occurred during the third and fourth weeks of the disease. Spinal fluid studies were made in 38 of the 47 patients. The findings were normal in all but 8 cases. There was no correlation between the prognosis for life or sequelae and the spinal fluid findings.

The prognosis in patients with cerebral complications in whooping cough depends upon the age of the patient, the severity of the paroxysm, the nutritional state of the patient, the length of the convulsive seizure, the duration of the coma, and upon the presence of an associated complication. In round figures, one third of the patients with cerebral complications die, one third recover with sequelae, and one third recover completely.

Twelve of the 28 surviving patients in this series were followed over periods ranging from 2 months to 8 years. Five (43 percent) of them showed a tendency toward the further manifestation of the central nervous system.

The pathologic changes in the brains of 34 autopsied patients with cerebral complications were edema and congestion of the brain, petechial hemorrhages, subarachnoid hemorrhages, and thrombosis of cerebral veins and sinuses. These changes may be considered due to vascular disturbances or degenerative changes incident to anoxemia rather than inflammatory in origin; no changes of an inflammatory nature were observed. The term "encephalopathy" appropriately covers these pathologic changes.

The treatment of cerebral complications in whooping cough is entirely symptomatic. There is no effective specific therapy. (J. Pediat., April '48 - A. M. Litvak et al.)

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Status of Immunization Procedures Against Pertussis: There have been many studies on pertussis vaccine but they differ from each other in many respects. Different methods of preparation of the vaccine, different dosages, different intervals between doses, and different study procedures have been used. The study procedures differ according to environmental groups studied, in adequacy of observation, in method of selection and treatment of controls, and in criteria for evaluating protection against pertussis. Thus, it is impossible to

make direct comparisons between the various studies, and no satisfactory conclusion can be made concerning which is the best product and what is the best method of administration. Considering each study separately, however, it can be safely concluded that certain vaccine products have given substantial protection against clinical pertussis and that other products have no demonstrated value.

The vaccines which have been shown to have value in field trials in the general population may be classified as fluid vaccines, alum-precipitated vaccines, and mixed vaccines. Of the fluid vaccines, there is good evidence that the fluid vaccine prepared as described by Doctor Kendrick has given substantial protection against clinical pertussis. Three or four doses of this product, representing a total of from 70 to 80 billion organisms, and given at weekly intervals to young children from 6 to 35 months of age, have demonstrated value. The difference in the method of preparation of this vaccine and that described by Doctor Sauer is probably of no great importance to their effectiveness for general use.

Of the alum-precipitated vaccines, there is good evidence that the A-P pertussis vaccine prepared as described by Doctor Harrison and his associates will give substantial protection against clinical pertussis. Three doses of this product, representing a total of 30 billion organisms given with a 1- and 3-week interval between doses to children from 6 to 35 months of age, have demonstrated value. Also, two doses of this product, representing a total of only 20 billion organisms and given with a 4-week interval between doses to children from 2 to 35 months of age, have given demonstrated protection. The A-P vaccine has been shown to be effective in young children of from 2 to 5 months of age.

Of the alum-precipitated mixtures of diphtheria toxoid and pertussis vaccine, an A-P mixture of pertussis vaccine and diphtheria toxoid, prepared as described by either Doctor Kendrick or by Doctor Bell, has similarly been shown to confer substantial protection against clinical pertussis. Three doses of this product, representing a total of 30 billion organisms and given with a 1- and 4-week interval between doses, gave protection against pertussis. The three doses of the A-P mixed product gave good protection against diphtheria as measured by blood-antitoxin titrations. Furthermore, two doses of the A-P mixed product, containing a total of 20 billion organisms and given with a 4-week interval between doses, gave substantial protection against clinical pertussis in children of from 2 to 5 months of age or of from 6 to 23 months of age. Incidentally, the two doses of the mixed product gave better protection against diphtheria than an equivalent amount of comparably given A-P diphtheria toxoid as measured by the Schick test.

Reactions reported due to the above-mentioned products have not been of sufficient significance to contraindicate their use. It is important to recall, however, that these products have not yet been used on the scale that diphtheria toxoid and smallpox vaccine are now employed. Long experience with other

and similar vaccines has shown that their benefit far outweighs their dangers. This seems likely with pertussis vaccine.

It is highly desirable that pertussis immunization should begin early in life, because the peak of deaths reported from this disease is at 2 months of age. Certain dangers attend the general use of an injection of any kind at this very young age. The death rate from all causes during the first few months of life is comparatively high; thus widespread use of any vaccine during the first few months of life requires caution lest some of the deaths due to usual causes may be wrongly attributed to the vaccine.

It is believed that there is sufficient evidence at hand to warrant public health officers' consideration of pertussis vaccine for general routine use. Such routine general use of pertussis vaccine should be limited to the products which have been shown to be effective in fulfilling the health officer's obligation to the community. (Am. J. Pub. Health, April '48 - J. A. Bell)

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An Epidemic of Diphtheria: An epidemic of diphtheria occurred in the state of Utah during 1947. Sporadic cases were reported from various areas during the first 10 months, but the great majority of cases occurred during late October, November, and the first part of December. Altogether there were 117 cases with 11 deaths, giving a case fatality rate of 9.4 percent, which is appreciably higher than the median case fatality rate of 6.25 percent for the 5-year period from 1941 to 1945 inclusive.

The causative organism was identified as the minimus type of Corynebacterium diphtheriae in 17 of the 93 cases in which the type of the organism was determined. This is considered to be the first time that the minimus type has been isolated in Utah. It has been isolated previously by Eller and Frobisher of Baltimore, Md., in 1944. The mitis type was identified as causative in 69 cases, the gravis in 6, and the intermedius in one. No deaths occurred in the mitis cases mentioned in this report.

Of the 100 cases in which the age was given, 73 percent occurred in children under 15 years of age and 27 percent in those over 15. Among the 93 patients in whom the causative type was isolated, immunization procedures had been carried out in 24 of the 69 mitis cases, in 10 of the 17 minimus cases, and in one of the 6 gravis cases. Previous workers including Eller and Frobisher have pointed out an increasing frequency of the occurrence of diphtheria among those having previously received immunizing injections. (Pub. Health Reps., 30 April '48 - A. A. Jenkins)

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Re Isolation of "Minimus" Type of Diphtheria Organisms: In the fall of 1947 T. W. Galbraith et al. of the Division of Laboratories, Utah State Department of Health, Salt Lake City, Utah, modified their tellurite medium so that it yielded a greater percentage of isolations and gave colonial characteristics which aided in differentiating between the gravis, mitis, and intermedius types of Corynebacterium diphtheriae. The gravis, mitis, and intermedius were the only types isolated until 20 November 1947 when a new type of colony was first seen. This colony was very small and would have been overlooked except for the routine use of a stereoscopic microscope at magnifications of 9X and 18X with reflected light.

Subcultures from these colonies in dextrose broth failed to produce acid within 7 days. Maltose, lactose, and sucrose broth cultures also remained alkaline. Intracutaneous inoculation of guinea pigs revealed that these organisms were of low virulence for that animal, producing only slight induration and but little erythema.

These characteristics led to the belief that this small colony type must be the minimus type described by Eller and Frobisher, Frobisher et al., and Frobisher in 1945 and 1946.

The following are the criteria the Utah laboratories are using for naming a given strain the minimus type:

On the modified tellurite medium, colonies are very small, from 0.2 to 0.3 mm. in diameter. Young colonies are effuse, with erose to lobulate margins, grey in color and dull in appearance. Older colonies on this medium are effuse but with a slightly raised circular ridge about one third of the way from the periphery, surrounding a crater-like depression. Stained smears from Loeffler's slants show the organism to be typically short, somewhat dumb-bell shaped, generally solid staining but sometimes barred but with no metachromatic granules observed. No acid was produced in dextrose broth in 72 hours. Some strains may ferment dextrose after prolonged incubation or several transfers. Maltose, lactose, and sucrose are not fermented. This organism is relatively avirulent as determined by intracutaneous inoculation (Fraser method) of guinea pigs, which produced only slight induration and erythema in them.

Since 20 November, diphtheria bacilli of all types have been isolated from 73 individuals. Of these, 39, or 53.3 percent, were of the minimus type and came from 14 separate communities. The clinical picture in patients from whom minimus strains have been isolated ranged from apparently normal to severe diphtheric infection including peripheral paralysis. Regional adenopathy, has occurred in a few cases, but not to the extent of being called "bull neck," and no deaths attributable to the minimus type have as yet been reported in Utah.

The fact that minimus strains were not recognized until 20 November 1947 does not prove that they had not been dealt with prior to that time.. Indeed, in

view of the fact that only recently did the laboratories modify their tellurite medium so that type differentiation became possible, it seems likely that this organism had not been recognized on many previous occasions. On the Difco medium, minimus colonies show no darkening and give little or no hint concerning their true nature. Although the morphological picture is not typical of Corynebacterium pseudodiphthericum, its usual fermentation pattern is, and the relative avirulence to guinea pigs would cause the unsuspecting bacteriologist to classify the organisms as C. pseudodiphthericum or C. xerosis.

If the above is true, and the authors believe that it is, there must be a great deal of diphtheria missed from the laboratory standpoint, and this may account for some of the discrepancies between the laboratory and the clinician. If this organism is about to come into prominence, it appears desirable that bacteriologists should employ routinely a tellurite medium capable of assisting in the differentiation of the various types of C. diphtheriae. That this organism is probably very widely spread appears probable, since Frobisher speaks of receiving four such strains from Leeds in 1936. He reports finding the minimus type in Baltimore in 1944, and it has been found in Utah in 1947. (Pub. Health Reps., 30 April '48)

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New Treatment in Cholera: Although the commoner sulfonamides or antibiotics have not been proved to be effective against cholera, a compound which in preliminary trials seems to have been effective has been produced by Bhatnagar and colleagues. The first observation was that hexamethylene-tetraamine in a 10-percent solution in physiological saline would kill Vibrio comma in vitro in less than half an hour. Crude compounds in which hexamine was linked with sulfanilamide were then prepared and in preliminary experiments gave promising results in animals and man. Later a condensation product containing two molecules of sulfathiazole and three molecules of formaldehyde was made. This compound has the formula $C_{21}H_{22}O_6N_6S_4$, but its structural formula has not yet been worked out; for the present it is termed Compound 6257. In vitro bactericidal action on Vibrio comma was well marked in concentrations of 50 mg. per 10 ml., and with lesser concentrations above 5 mg. per 10 ml. there was bacteriostatic activity. The in-vitro tests were confirmed in mice inoculated intraperitoneally with 2 M.L.D. of Vibrio comma. When mice were given 40 or 50 mg. of the drug in divided doses for two days prior to inoculation and then the same dose morning and evening for four days after inoculation, there was complete protection if the drug was given subcutaneously or intraperitoneally. If given by mouth, the drug saved only 10 percent of mice, presumably because of poor absorption from the alimentary tract.

Field trials were carried out in the Tanjore District of Southern India on cholera patients who were for the most part undernourished women and children suffering from the effects of purgation, vomiting, and suppression of urine. A specimen of stools was first examined to establish the diagnosis, and the drug

was then given in a dose of 6 Gm., followed 4 hours later by 4 Gm. - usually by mouth, though if vomiting were profuse the drug was administered per rectum. Usually the total dosage was 28 Gm., of which 10 Gm. was given on the first day, two doses of 4 Gm. on the second day, and thereafter two doses of 1 Gm., morning and evening, for the next five days. From 6 to 8 hours after starting treatment, purgation became less and vomiting ceased. By the ninth hour, as a rule, the patient had passed urine, although in 3 seriously ill patients it took from 20 to 24 hours. Nourishment in the form of barley or rice "kunji" (decoction) greatly helped to restore the kidney function.

There was distinct improvement by the end of 24 hours. Purgation was much reduced, and nausea, vomiting, and cramps were absent. Although the patient was weak and dehydrated, the pulse was perceptible and interest was taken in the surroundings. By the 48th hour the body was warm and dehydration was reduced in proportion to the fluid taken (which was insisted upon). By the morning of the fourth day the patient was convalescent and well on the way to recovery. Vibrio comma was absent from the stools on the sixth day.

So far 85 patients with bacteriologically proved cholera have been treated under field conditions in 27 villages, with a mortality of only 4 percent - in contrast to the usual mortality during the past seven years of 60 percent. No toxic manifestations have been seen even when as much as 50 Gm. of this compound has been given. Plenty of water, however, was drunk by the patients, and soda water when available. Although no details are given, it is said that the drug has been remarkably effective when administered prophylactically to those in contact with the disease in villages where there is infection. If these results are confirmed, a considerable advance in the chemotherapy of cholera has been made. (Annotation, Brit. M. J., 3 April '48)

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Penicillin and Sulfathiazole in Typhoid Fever: Considerable interest was aroused when Bigger found that typhoid bacilli are killed, or effectively inhibited, in the test-tube by the combined action of penicillin and sulfathiazole. Bigger suggested that typhoid fever might be treated with a combination of the two drugs, and McSweeney followed this suggestion and claimed good results in a few patients treated in this way. (See News Letter of 30 August 1946, page 2.)

The typhoid outbreak that occurred in Aberystwyth, Wales, in July and August, 1946, offered an opportunity for a trial of the combined penicillin-sulfathiazole treatment.

Of 39 patients who received courses of treatment similar to those adopted by McSweeney, most were treated in the second and third weeks, as were also McSweeney's patients. The authors did not observe the speedy disappearance of toxemia and subsidence of pyrexia described by McSweeney.

Three small groups of patients treated with penicillin-sulfathiazole were compared with three untreated control groups, and there was no evidence of an appreciable clinical effect of the drug treatment.

There were no fatalities in the largest group of 25 treated patients, but 5 of those whose condition caused the greatest anxiety had been given Felix's "Vi + O" antityphoid serum.

A considerable proportion of patients yielded positive blood cultures shortly after completion of their courses of penicillin-sulfathiazole treatment.

Fecal excretion of Eberthella typhosa during convalescence was not shorter in the treated groups than in the controls. In one of the treated groups there was no evidence of even a temporary disappearance of E. typhosa from the feces.

The strain of organism responsible for the Aberystwyth outbreak was not more resistant to the action of penicillin and sulfathiazole than were four other strains with which it was compared in in-vitro tests.

Because of the complications likely to develop as a result of the large doses involved, the authors consider it necessary to warn against the indiscriminate use of penicillin-sulfathiazole in the treatment of typhoid fever. (Lancet, 10 April '48 - G. Bevan et al.)

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Hemophilia: One of the wartime publications of the Institute of Human Genetics of the University of Copenhagen deals with hemophilia. In this study, Andreassen set out to discover every person in Denmark who was known to suffer from hemophilia, including those recently dead. The total number of families was 63, containing 205 hemophiliacs. The frequency of the disease in males (if we allow an average length of life one third of that of normal males) is 1.3 per 10,000. Haldane pointed out that the rate of elimination of the gene for hemophilia must be considerable, for one third of such genes are in the x-chromosomes of affected males, who tend on the average to be of low fertility. The loss of genes is balanced by fresh mutation, and the life of the average hemophilia gene, once it has appeared by mutation, is not much more than about three generations. Andreassen's estimate of the mutation rate is 1 in 53,000 per x-chromosome per generation.

In this study, Andreassen developed a technic (originally used by Burker) for the measurement of coagulation time. The essential feature of the method is the determination of the end point of coagulation. He has thus been able, for the first time, to demonstrate unequivocally a difference between normal blood and the blood of the heterozygous female carrier. The average coagulation time of blood taken from 81 normal individuals was 8.2 minutes, but in the case of 19 known carriers it was 16 minutes. Actually, there was no overlapping, the

longest normal time being 10 minutes and the shortest carrier time 10.5. It has often been suggested that carrier women may be somewhat more prone to bleeding than the normal, a subject about which Andreassen is cautious, but his observation tends to confirm this view. Incidentally he agrees that there is no authentic case of a female hemophiliac; in the very rare instances in which the appropriate genetic constitution might have been present a dose of the gene on both x-chromosomes has presumably led to a non-viable embryo. The practical importance of this work, if the technic yields equally good results in the hands of the general pathologist, is the help it offers to the sister of a hemophiliac. At present such a woman can be told only that there is a 50-percent chance that she is a carrier. It would be a great advance if half the sisters of hemophiliacs could be told that they are free of the gene and can safely have children.

Haldane has made a detailed study of Andreassen's data, and, though in the main confirming his conclusions, considers that they should be modified in certain respects. Andreassen estimates the fertility of hemophilic men as 0.57 of the normal; Haldane arrives at the lower figure of 0.29. Instead of a frequency of mutation of 1 in 53,000 x-chromosomes per generation, Haldane gives an estimate of 1 in 31,000. Haldane draws a further interesting conclusion. The great majority of mothers of hemophiliacs, even of sporadic ones, i.e., those due to a recent mutation, prove to be heterozygous. This means that the mutation must have occurred a generation earlier. Thus it would appear that the mutation rate is considerably greater in men than in women. In the normal course of events a mutation occurs in the x-chromosome of a man who hands on the mutant gene to a daughter; the trait then becomes manifest for the first time in her sons. From the practical point of view this is unfortunate, for the great majority of sisters of hemophiliacs have the ordinary 50-percent chance of being carriers even when the affected brother is the first hemophiliac to appear in the family group. (Annotation, Brit. M. J., 10 April '48)

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A Procedure in Rodent Control: The quarterly report of rodent control operations required by BuMed C/L 48-18 has been received from a large number of activities. This report shows that there has been considerable interest at some stations in developing methods to meet local requirements. One noteworthy method might be found to be useful at other stations.

The rodent control officer at the U. S. Marine Corps Air Station, Cherry Point, N. C., has developed a method of "smoking out" nests and burrows underneath buildings which at the same time apparently destroys rodent fleas and certain other ectoparasites. A lengthy section of rubber hose is attached to the exhaust pipe of one of the DDT fogging jeeps (exhaust-generator equipment) and, with the fogging equipment turned on, the distal end of the hose is placed in openings of rodent burrows. The exhaust contains the DDT-in-oil fog mixed with the carbon monoxide and other products of combustion from the jeep engine.

It is reported that this treatment forces rodents from their burrows and aids in locating all burrow openings which are then secured with tamped earth or other available material. (Preventive Medicine Div., BuMed)

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Procedure for Accurate Duplication of Master Denture Models: In the process of fabricating a series of metal horseshoe-shaped partial upper dentures, it was found that a number of these castings did not fit the master model or the mouth, particularly in the palatal areas. A discrepancy of from 1 to 3 millimeters between the casting and the palatal tissues was noted.

A study of the procedures involved revealed that a distorted casting investment model, particularly in the palatal areas, was produced by a too rapid cooling of the hydrocolloidal duplicating material.

In order to reproduce a master model most accurately, particularly when the ring-shaped duplicating flask is used, it is important to bench-cool the hydrocolloidal material until the initial set has taken place, after which the flask containing the material may be placed in a shallow container of cold water. Not more than one fourth of the flask should be in the water. After the hydrocolloidal material is cold to the touch, the entire flask may be immersed in cold water for final chilling. By following this method of slow cooling, distortion of the hydrocolloidal mold may be minimized or eliminated with a resultant investment model that is a more accurate reproduction of the master model. (U. S. Naval Dental School, Bethesda, Md.)

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Relative Efficiency of Goggles for Dark Adaptation: How best to secure dark adaptation is an important problem in active service and in any night vision test. The procedure adopted by the Navy has been to have a subject wear red goggles for 20 minutes and follow this by 10 minutes in the dark. This method is being used in Research Project NM 003 024 in conjunction with which the present study was undertaken to determine the relative dark adaptation-promoting efficiency of several types of goggles and the effectiveness of goggles in general for this purpose. The acceptance of red filters as an adaptive device by the Armed Services.and by many experimenters in night vision makes it desirable to compare them with neutral filters.

The relative efficiency of three types of goggles in securing dark adaptation was measured and the effectiveness of goggles in general evaluated in order to be able to use the most efficient device for dark-adapting observers.

Measurements were made with 19 observers under two conditions of light adaptations: Series I: 5 minutes of light at 15 mL brightness followed by 20 minutes of goggle adaptation at the same brightness, and Series II: 10 minutes

of light at 300 mL brightness followed by 20 minutes of goggle adaptation at that brightness.

Effectiveness of goggle adaptation was measured in terms of the time needed to attain two specific levels of scotopic sensitivity, namely, the capacity to see an area at 4.14 log$\mu\mu$L (micromicronlamberts) luminance and one at 3.34 log$\mu\mu$L. These brightnesses correspond roughly to "overcast starlight" and to "very dark overcast night."

Navy red goggles proved most effective in securing dark adaptation to the brightness levels used; the "browrest" red goggles stood next in efficiency, and the neutral filters were least effective, although the differences were not large.

The finding that neutral goggles were consistently inferior to either of the red types under all conditions of the experiment supports the view that the red goggles, by virtue of their lower scotopic transmission values, are superior to neutral filters for dark adaptation purposes.

Adaptation with any of the types of goggles used in the study shortens the time in the dark room required for a given level of dark adaptation, the amount of time saved depending on the initial adaptation level and the level of dark adaptation it is desired to attain. The higher the initial adaptation level is, the greater the relative effectiveness of red goggles.

The general usefulness of goggles in dark adaptation is dependent upon the activities required of the adapting individual. Only if he gains by being occupied while adapting are goggles a time saver. If he must reach a certain level of dark adaptation in the shortest possible time, total darkness is more effective.

For fluoroscopic and photographic work in dark rooms, the small bulk and the wearing comfort of "browrest" goggles outweigh their slightly lower efficiency. (NM 003 024 (X-757 (Av-387-k)), Prog. Rep. No. 1, 9 April '48, Medical Res. Lab., Sub. Base, New London - Z. J. Schoen and F. L. Dimmick)

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Further Study of BCG Vaccination: At the 1946 conference on BCG vaccination, held in Washington in September of that year, certain recommendations were made which were reported in the 7 March 1947 issue of Public Health Reports. Since that time, nation-wide interest in this immunizing procedure has grown to an unprecedented level of intensity. The demand from every quarter for additional information concerning the course of BCG investigations was such that an evaluation and review of recent work in the field became increasingly appropriate. To that end, a second conference was held in New York City on 9 March 1948, attended by the same group which had met in 1946 to formulate the original policy.

In considering the present status of BCG, the New York conference recognized that many fundamental problems are yet to be resolved concerning the vaccination technic and the vaccine itself. Accordingly, the committee of specialists recommended that the entire problem of BCG continue to receive further attention in the form of intensified research and critical study, and that its application in this country be restricted to certain groups and circumstances.

The results of careful study leave little doubt that BCG is harmless. As for the degree of immunity which the agent confers, however, there has been very little unanimity of opinion. Although it has become increasingly evident that properly administered BCG vaccination does increase individual resistance to tuberculous infection, there is still a singular lack of definitive information concerning the exact duration of the protection bestowed by the agent. The reason for this is simply that to date, there has been no reliable study of sufficient duration to permit precise evaluation of the vaccine's effectiveness over long periods of time.

Should further study demonstrate that BCG vaccination confers only short-term protection, this would not necessarily argue against its use, for revaccination would serve to re-establish protection, which procedure is necessary in the case of certain other immunizing agents.

Regardless of the ultimate place of this immunizing agent in the nation's tuberculosis control program, however, it is extremely unlikely that BCG will ever obviate entirely the necessity for the conscientious prosecution of proved control measures. These must be exploited to the fullest in order to secure past gains and to meet present needs. Indeed, there is a considerable body of opinion in this country which holds that modern methods of diagnosis and treatment make possible the effective control of the disease without resort to vaccination procedures, especially in areas of low prevalence which possess adequate facilities for diagnosis and medical care.

Until all the problems incident to BCG vaccination as a tuberculosis control technic are resolved, and until the implications of a change in emphasis become clear, efforts in the application of measures which long experience has shown to be eminently practical and profitable should not be relaxed. (Editorial, 7 May '48, Pub. Health Reps. - F. J. Weber)

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List of Civilian Medical Institutions Utilized for Training of Naval Medical Officers: In order to inform medical officers of the scope of the Graduate Medical Training Program of the Bureau of Medicine and Surgery, a listing of civilian institutions in which training is available to Medical Officers of the regular Navy is herewith presented. The training opportunities included in this list are in addition to those available in Naval hospitals.

In view of the large number of officers requesting training and the limited number that may be made available and placed in training at any one time, requests should be submitted three or four months prior to the beginning date of training requested. Requests may be submitted by despatch if the necessary service agreements follow by regular mail, and when the time limit involved warrants a despatch request.

In general, the application for training should be submitted in accordance with the Outline published in the News Letter dated 23 May 1947, page 22.

Inquiries regarding graduate medical training may be directed to the Bureau of Medicine and Surgery (Attention: Professional Division) at any time.

TRAINING IN CIVILIAN INSTITUTIONS

No. of Places	Institution	Specialty	Type of Training	Duration	Starts
		ALLERGY			
1	University of Illinois		Course	12 Months	10-1-48
		ANESTHESIA			
1	Memorial Hospital, NYC		Residency	12 Months	Any time
1	Memorial Hospital, NYC		Residency	24 Months	Any time
3	Mayo Clinic		Fellowship	12 Months	Every Quarter
1	Huron Road Hosp., Cleveland		Residency	24 Months	1-1-50
1	George Wash. Univ.		Residency	12 Months	1-1-49
1	Univ. of Chicago		Residency	12 Months	Any time
1	Cleveland Clinic		Residency	24 Months	Any time
		BIO-PHYSICS			
1	Univ. of Penn. (Filled)		Course	36 Months	7-1-48
		CARDIOLOGY			
1	Mass. General Hospital		Preceptor-ship	12 Months	10-1-48

No. of Places	Institution	Specialty	Type of Training	Duration	Starts
		DERMATOLOGY & SYPHILOLOGY			
2	Skin & Cancer Unit of New York Postgraduate School, NY Univ.		Course	11 Months	10-1-48
1	Harvard University		Course	11 Months	10-1-48
2	Univ. of Pennsylvania		Course	8 Months	10-1-48
1	Washington Univ. St. Louis (Filled)		Course	12 Months	10-1-48
		DISEASES OF THE CHEST			
*4	Trudeau School of Tuberculosis		Course	4 Weeks	9-13-48
*4	Bellevue Hosp., NYC		Course	2 Weeks	10-11-48
	*Course runs concurrently				
		ELECTROENCEPHALOGRAPHY			
4	National Naval Medical Center, Bethesda, Md.		Course	6 Months	7-1-48
		ENDAURAL FENESTRATION			
1	Lempert Otological Inst. (Open only to Diplomates of American Board of Otolaryngology)		Course	6 Weeks	Any time
		GASTROENTEROLOGY			
1	Univ. of Pennsylvania		Course	12 Months	10-1-48
		HAZARDS OF NUCLEAR RADIATION			
5	Univ. of Chicago		Course	6 Months	10-1-48
3	Univ. of Rochester		Course	8 Months	9-30-48
		INTERNAL MEDICINE			
1	Boston City Hosp. (Filled)		Residency	12 Months	7-1-48
1	Northwestern Univ. (Cook County Hospital)		Course	12 Months	7-1-48
1	Northwestern Univ. (Cook County Hospital)		Course	12 Months	1-1-49
1	State Univ. of Iowa		Course	12 Months	10-1-48
4	Univ. of Pennsylvania (Filled)		Course	8 Months	10-1-48
3	Cornell Univ. Medical School (Intensive Course)		Course	6 Months	10-1-48
1	Mayo Clinic		Fellowship	12 Months	10-1-48
1	New York Hospital, NYC		Fellowship	12 Months	10-1-48
1	Peter Bent Brigham Hosp. (Filled)		Residency	12 Months	7-1-48
1	Tulane Univ. (Int. & Trop. Med.)		Course	24 Months	10-1-49
1	Strong Memorial Hospital		Residency	12 Months	7-1-48

No. of Places	Institution	Specialty	Type of Training	Duration	Starts
		NEUROSURGERY			
1	Albany Hospital (Filled)		Residency	24 Months	7-1-48
1	Marquette Univ.		Preceptorship	12 Months	Any time
1	Massachusetts General Hospital		Preceptorship	24 Months	7-1-48
1	Lahey Clinic		Fellowship	12 Months	10-1-48
1	Univ. of California		Fellowship	24 Months	7-1-49
		OBSTETRICS & GYNECOLOGY			
1	Harvard Univ. (Filled)		Residency	12 Months	8-1-48
2	Univ. of Pennsylvania		Course	8 Months	10-1-48
1	Columbia Hosp., Wash., D. C.		Residency	18 Months	7-1-49
1	St. Joseph Infirmary, Houston		Residency	12 Months	3-1-49
		ONCOLOGY			
1	Memorial Hospital, NYC (Surgery)		Asst. Residency	18 Months	1-1-49
1	Memorial Hospital, NYC (Special)		Grad. Fellowship	12 Months	7-1-48
		OPHTHALMOLOGY			
1	State Univ. of Iowa		Residency	24 Months	9-1-49
1	Univ. of Pennsylvania		Course	8 Months	10-1-48
2	Washington Univ. St. Louis (2nd year level)		Course	8 Months	10-1-48
1	Illinois Eye & Ear Inf. (Filled)		Course	12 Months	7-1-48
1	Tulane Univ.		Course	12 Months	7-1-48
1	Boston City Hospital		Internship	12 Months	10-1-49
1	Northwestern Univ. (Filled)		Course	9 Months	10-1-48
1	Mass. Eye & Ear Inf. (Filled) (Competitive Exam. only)		Residency	27 Months	9-29-47
		ORTHOPEDICS			
1	Lahey Clinic (Filled)		Fellowship	12 Months	10-1-48
1	Cleveland Clinic (Filled)		Fellowship	12 Months	7-1-48
1	NY Orthopedic Disp. & Hosp. (Filled)		Residency	24 Months	12-1-48
		ORTHOPEDICS (Children's)			
1	Shriner's Hosp., Phila., Pa. (Filled)		Residency	12 Months	7-1-48
1	James W. Riley Memorial Hosp., U. Ind.		Residency	12 Months	1-1-49
1	Duke Univ.		Residency	12 Months	1-1-49
1	Univ. of Oklahoma		Residency	12 Months	1-1-49
1	St. Charles Hosp., NYC (Filled)		Residency	12 Months	7-1-48
1	Children's Hosp., Boston, Mass.		Residency	12 Months	1-1-49
1	State Univ. of Iowa		Course	10 Months	9-1-48
1	Alfred I. DuPont Inst.		Residency	12 Months	1-1-49

No. of Places	Institution	Specialty	Type of Training	Duration	Starts
		OTOLARYNGOLOGY			
1	New York Hospital, NYC		Fellowship	12 Months	3-1-49
1	Univ. of Illinois		Course	9 Months	10-1-48
1	Washington Univ., St. Louis		Fellowship	8 Months	10-1-48
1	Washington Univ., St. Louis (Filled)		Residency	12 Months	7-1-48
2	Univ. of Pennsylvania		Course	8 Months	10-1-48
		PATHOLOGY			
1	Memorial Hospital, NYC (Filled)		Fellowship	12 Months	7-1-48
1	Mayo Clinic		Fellowship	12 Months	1-1-49
1	Univ. of Pennsylvania (Filled)		Residency	36 Months	10-1-47
1	Northwestern Univ.		Course	12 Months	7-1-48
1	Indiana Univ.		Fellowship	12 Months	7-1-48
1	Henry Ford Hospital (Filled)		Fellowship	12 Months	7-1-48
1	Wayne Univ. Med. College (Filled) (2nd year level)		Fellowship	12 Months	10-1-48
1	Univ. of Michigan (Filled) (3rd year level)		Fellowship	12 Months	7-1-48
1	Long Island College of Med.		Fellowship	18 Months	5-1-49
		PEDIATRICS			
1	Children's Hospital, Boston, Mass. (Filled)		Residency	12 Months	7-1-48
1	Children's Hospital, Philadelphia		Residency	9 Months	1-1-49
2	Univ. of Pennsylvania		Course	8 Months	10-7-48
1	Children's Hosp., Detroit (Filled)		Course	12 Months	7-1-48
1	Johns Hopkins Univ. (Filled)		Residency	12 Months	7-1-48
		PHYSICAL MEDICINE			
2	Mayo Clinic		Fellowship	12 Months	Every Quarter
		PLASTIC SURGERY			
1	Memphis Hospitals		Fellowship	12 Months	1-1-49
		PSYCHIATRY			
1	Colorado Psych. Hospital		Residency	12 Months	7-1-48
1	Univ. of Louisville		Fellowship	12 Months	Any time
3	St. Elizabeths Hospital		Residency	12 Months	10-1-48
1	Payne Whitney Psych. Div., New York Hosp., NYC		Fellowship	12 Months	6-1-48
1	Langley Porter Clinic, Univ. of Calif.		Fellowship	12 Months	4-1-49

No. of Places	Institution	Specialty	Type of Training	Duration	Starts
		PSYCHIATRY (Cont'd)			
2	Institute of Penn. Hosp. (For Flight Surgeons)		Fellowship	12 Months	9-1-48
1	Institute of Penn. Hosp.		Fellowship	12 Months	7-1-48
1	Philadelphia Child Guidance Clinic		Fellowship	10 Months	10-1-48
1	Illinois Psych. Inst., Univ. of Ill.		Course	12 Months	4-1-49
1	Johns Hopkins Univ. (Filled)		Fellowship	12 Months	7-1-48
1	NY Psychiatric Inst.		Fellowship	12 Months	7-1-48
		NEUROLOGY			
1	NY Neurological Inst. (Filled)		Fellowship	12 Months	6-1-48
1	Jefferson Hosp., Phila., Pa.		Fellowship	12 Months	7-1-48
		PHYSIOLOGY			
1	University of So. Calif. (Concerned mainly with the Physiology of Acceleration) (Flight Surgeons Only)		Course	9 Months	10-1-48
		PUBLIC HEALTH*			
2	Harvard Univ. (Filled)		Course	11 Months	9-15-48
1	Johns Hopkins University (V-D Control) (Filled)		Assistant-ship	11 Months	7-1-48
3	Johns Hopkins University (Preventive Medicine)		Course	8 Months	10-1-48
2	Johns Hopkins University (Medical Statistics)		Course	8 Months	10-1-48
1	Johns Hopkins University (Filled)		Course	16 Months	1-30-48
1	Tulane University		Course	12 Months	10-1-48
	*All leading to the Degree of Master of Public Health.				
		RADIOLOGICAL SAFETY			
2	Univ. of California (Arranged upon request)		Course	12 Months	Any time
		RADIOLOGY			
1	Univ. of Chicago (Filled)		Fellowship	12 Months	9-1-48
1	Mayo Clinic		Fellowship	18 Months	10-1-48
1	Johns Hopkins University		Fellowship	12 Months	7-1-48
1	Washington Univ., St. Louis		Fellowship	12 Months	7-1-48
1	New York Hospital, NYC		Fellowship	12 Months	7-1-48
1	Lahey Clinic		Fellowship	12 Months	10-1-48
1	Harper Hospital, Detroit		Fellowship	12 Months	1-1-49
1	State University of Iowa (Therapy only)		Course	12 Months	7-1-48

No. of Places	Institution	Specialty	Type of Training	Duration	Starts
		RADIOLOGY (Cont'd)			
1	Henry Ford Hospital		Fellowship	12 Months	10-1-48
1	University of Pennsylvania		Course	8 Months	10-1-48
1	Union Memorial Hospital, Baltimore, Md.		Fellowship	12 Months	Any time
		RESEARCH (Pathology of Liver)			
1	Univ. of Pennsylvania		Course	24 Months	9-15-49
		STAFF COLLEGE (Captains & Commanders only)			
1	Industrial College of the Armed Forces, Washington, D. C.		Course	10 Months	9-2-48
		SURGERY			
2	Georgetown Univ. Hosp.		Fellowship	12 Months	9-1-48
1	Cleveland Clinic		Fellowship	24 Months	10-1-49
6	Univ. of Pennsylvania		Course	8 Months	10-1-48
1	State Univ. of Iowa		Fellowship	12 Months	10-1-48
2	Lahey Clinic		Fellowship	12 Months	10-1-48
1	College of Medical Evangelists		Course	8 Months	10-1-48
1	Northwestern University		Fellowship	12 Months	7-1-48
1	Northwestern University		Fellowship	12 Months	1-1-49
		THORACIC SURGERY			
1	Univ. of Michigan		Fellowship	24 Months	10-1-49
		UROLOGY			
1	Stanford Univ. Hospital (Filled)		Residency	31 Months	12-1-47
1	James B. Brady Fdt. (Filled)		Fellowship	12 Months	7-1-48
1	Washington Univ., St. Louis		Fellowship	12 Months	10-1-48
1	Tulane University		Fellowship	12 Months	1-1-49
1	Univ. of Pennsylvania (Filled)		Course	8 Months	10-7-48
1	University of Michigan		Fellowship	12 Months	7-1-48
		LAW			
1	George Washington University (1 officer will be started in Law each year)		Course	36 Months	10-1-48

(Professional Div., BuMed)

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Openings in Research, the New Navy Specialty: In order to develop a well integrated group of Naval medical research specialists, the Bureau of Medicine and Surgery has added the field of "research" to the list of Naval medical specialties for which officers of the Naval Medical Corps, Dental Corps, and Medical Allied Sciences Section of the Medical Service Corps may qualify. Prior to this, officers who were interested in research were assigned to this duty, but there was no assurance that they would be retained in such a billet longer than the normal tour of duty or receive subsequently such duty assignments. Those assigned in this new specialty are assured of spending a major part of their Naval career in research billets.

The qualifications required for this specialty are not inflexible, but it is desirable to have a PhD degree in one of the medical sciences such as bacteriology, biochemistry, physiology, psychophysiology, biophysics, etc., or in one of the sciences allied to medicine such as entomology, helminthology, mammalogy, etc. Officers qualified in one of the medical sciences, and having some knowledge or experience in an engineering field would be considered especially well suited for certain types of important Naval medical research projects. The Bureau points out that although previous experience in research is preferred, the application of any officer of the Navy (including active and inactive Reserves) having an interest in medical research as a career will be considered. If training is indicated for selected applicants, they will be started in a tour of duty at one of the Naval medical research institutions, probably at Bethesda, Maryland, followed later in their career by a short tour of sea duty to provide an over-all picture of the Navy's needs and point of view. Training will also be offered in civilian research laboratories, in many of which the Navy sponsors and underwrites many research projects.

There will be adequate opportunity for experience in many different subjects. Every attempt will be made to allow as much freedom as possible in the choice of investigative projects provided that the expected results will contribute to the total of scientific knowledge and to the specific needs of Naval medicine.

In addition to the Naval Medical Research Institute at Bethesda, Maryland, the Navy maintains six other research units. These are the Naval Medical Research Units I, III, and IV, at Berkeley, California, Cairo, Egypt, and Great Lakes, Illinois, respectively; the Naval School of Aviation Medicine and Research at Pensacola, Florida; the Naval Medical Research Laboratory at New London, Connecticut; and the Naval Medical Field Research Laboratory at Camp Lejeune, North Carolina.

Applications are desired from officers of the regular Navy, the Naval Reserve (active and inactive), and from qualified civilian physicians, dentists, and scientists interested in a career in Naval medical research. (Public Relations and Personnel Divisions, BuMed)

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Obligated Service Regarding the Graduate Medical Training Program: It has been brought to the attention of the Professional Division of BuMed that numerous medical officers are under the impression that if they receive training which makes them eligible for Board Certification, they are automatically obligated for the three years of service after they become certified. In order to clarify the understanding concerning the amount of service obligatory for those taking part in the training program, the following excerpts from the Outline of the Graduate Training Program in the Navy Medical Corps, dated 15 November 1947, are presented:

"4. Recipients of graduate medical training are expected to remain in the Navy for the periods indicated below:

a. Residencies in Naval Hospitals (The same service agreements pertain to residencies in other Federal hospitals.)

(1) For one year of residency training in a Naval Hospital, the candidate shall agree not to resign during the residency and to remain in the Navy for one year following completion of the residency.

(2) For two consecutive years of residency training in a Naval Hospital, the candidate shall agree not to resign during the residency and to remain in the Navy for two years following the completion of the two years of residency training.

(3) For three consecutive years of residency training the candidate shall sign an agreement not to resign during the residency and to remain in the Navy for three years following completion of the three years of residency training.

(4) Unapproved residencies require no service agreement.

b. Training in Civilian Institutions

(1) Applicants for courses of 6-12 months' duration shall be required to sign an agreement not to resign during

the course and to remain in the Navy for a period of three years following completion of the course of instruction.

(2) One additional year of obligated service shall be required for each consecutive six months of training beyond the one year. Example: 1 and 1/2 years = 4 years; 2 years = 5 years; 2 and 1/2 years = 6 years; 3 years = 7 years of obligated service following completion of the course, fellowship, or residency."

A Naval medical officer is therefore only obligated for the training he receives as listed above. Passing his Specialty Board examination and becoming certified does not further obligate him in any manner or alter any service obligations he may already have. (Professional Div., BuMed)

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Circular Letter 48-50

3 May 1948

To: All Ships and Stations

Subj: Medical Department Money Allotments, Fiscal Year 1949

Refs: (a) BuMed C/L 47-68 AS&SL Jan-June 1947, 47-501, page 267.
(b) SecNav ltr dtd 19 Sept 1947; ND Bulletin of 30 Sept 1947, 47-882.
(c) BuMed C/L 45-178; AS&SL July-Dec 1945, 45-801, page 342.
(d) BuMed C/L 48-24; ND Bulletin 29 Feb 1948, 48-117.
(e) BuMed C/L 48-26; ND Bulletin 15 March 1948, 48-165.

This letter contains information and instructions concerning Medical Department Money Allotments, for vessels of the Navy for the fiscal year 1949. Reference (a) is cancelled.

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Circular Letter 48-51

6 May 1948

To: Commandants Naval Districts (Less 10) and Potomac River Naval Command.
Attn: District Director of Naval Reserve and District Director of Training.

Subj: First-Aid Supplies for Naval Reserve Electronic Warfare Drill Quarters and Electronic Warfare Stations.

This letter authorizes certain first-aid supplies for subject facilities and gives information and instructions concerning requisitions and appropriations against which the supplies are to be charged.

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Circular Letter 48-52

7 May 1948

To: All Ships and Stations

Subj: Accounting Procedures for Unit Pricing of Medical Department Property.

Refs: (a) BuMed C/L 46-79 dated 13 May 1946 (No. 46-1018 Navy Department Bulletin of 15 May 1946).
(b) ALNAV 185 dated 26 August 1947.
(c) Chapter 3, Vol. VI - BuSandA Manual.
(d) Army and Navy Catalog of Medical Materiel.

This letter cancels reference (a) and sets forth accounting procedures for Medical Department property that are to become effective 1 July 1948. A full copy of this letter appears in the Navy Department Bulletin of 15 May 1948.

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Circular Letter 48-53 10 May 1948

To: All Naval Hospitals

Subj: Unit Price Adjustments Affecting Statement of Storeroom Inventories, F.Y. 1948.

Ref: (a) Cir. Ltr 46-79 dated 13 May 1946.

This letter states that a review of the first and second quarterly financial reports reveals discrepancies in reporting Unit Price adjustments on the Statement of Storeroom Inventories, insofar as equipment is concerned, and gives a procedure for remedying the discrepancies at the close of the fourth quarter.

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Circular Letter 48-54 12 May 1948

To: All Naval Stations

Subj: Medical Training Films and Other Medical Audio and Visual Aids, Report of.

Ref: (a) BuMed CirLtr No. 48-17 of 12 Feb 1948, N.D. Bull. of 15 Feb 1948, 48-86, p. 20.

This letter directs (1) that addressees that have not submitted subject report required by reference (a) do so immediately and (2) that addressees that submitted incomplete reports resubmit complete ones.

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